

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Patent Application No. 10/526,697

Applicant: Mark E. DUDLEY et al.

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Examiner: Michail A. Belyavskiy

Docket No.: 233876

Customer No.: 45733

Commissioner for Patents  
U.S. Patent and Trademark Office  
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Alexandria, VA 22314

**REPLY BRIEF**

Sir:

In reply to the Examiner's Answer dated April 6, 2010, please consider the following remarks.

**Remarks/Arguments** begin on page 2 of this paper.

*REMARKS/ARGUMENTS*

In response to the Examiner's Answer dated April 6, 2010, please consider the following remarks.

**I. No *prima facie* case of obviousness has been established because the combination of Dudley 2001, WO '239, Slavin, Riddell, Rosenberg, Kawakami, and Stevens fails to teach or suggest administering T cells which have undergone *one* cycle of rapid expansion, as claimed.**

Appealed claim 23 is directed to a method comprising, *inter alia*, administering T cells which have undergone *one* cycle of rapid expansion. The Office Action dated December 17, 2008 and the Examiner's Answer acknowledge that Dudley 2001 and WO '239 fail to teach administering T cells which have been subjected to one cycle of rapid expansion. Nevertheless, the Office Action dated December 17, 2008 (page 5, ¶ 2) and the Examiner's Answer (page 5, ¶ 3) state that "[a]ll of the claimed elements were known in the prior art" (emphasis added).

This is incorrect because *none* of the cited references, Dudley 2001, WO '239, Slavin, Riddell, Rosenberg, Kawakami, and Stevens, teach administering T cells which have been subjected to *one* cycle of rapid expansion, as claimed. Therefore, the cited combination of references fails to teach or suggest administering T cells which have undergone one cycle of rapid expansion. The Examiner fails to even so much as allege where the prior art teaches administering T cells which have been subjected to *one* cycle of rapid expansion, as claimed. Accordingly, a *prima facie* case of obviousness has not been made, and the obviousness rejection cannot stand.

**A. Riddell teaches away from using one cycle of rapid expansion.**

The obviousness rejection cannot stand because Riddell teaches away from using one cycle of rapid expansion.

The Examiner's Answer (page 14, ¶ 1) states that "[n]owhere do Riddell et al., teach that multiple rounds of rapid expansion should be used for adoptive immunotherapy."

On the contrary, Riddell specifically teaches *repetitive* expansion and recommends this method to provide sufficient cell numbers for adoptive immunotherapy. Accordingly, one of ordinary skill in the art reading Riddell would not expect that a single rapid expansion would generate large enough numbers of T cells for successful adoptive immunotherapy. Therefore, Riddell teaches away from the use of one cycle of rapid expansion, as claimed, and the obviousness rejection based in whole or in part on Riddell cannot stand.

**II. Any alleged *prima facie* case of obviousness is rebutted by the Appellants' evidence of unexpectedly superior clinical results, long-felt need, and repeated failure of other methods.**

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been set forth (which the Appellants maintain has not been set forth), the Examiner fails to show why *all* of the Appellants' rebuttal evidence regarding secondary considerations, particularly the Declaration under 37 CFR § 1.132 by Dr. Mark E. Dudley (Appeal Brief, Exhibit A, hereinafter, "Dudley Declaration") filed on October 17, 2008, fails to rebut any alleged *prima facie* case of obviousness.

**A. The Dudley Declaration is evidence that the claimed method provides unexpectedly superior clinical results as compared to prior art methods.**

The obviousness rejection cannot stand because the Dudley Declaration evidences that the claimed method provides unexpectedly superior clinical results as compared to prior art methods, contrary to the expectations of one of ordinary skill in the art.

The Examiner's Answer (page 11, ¶ 4) states that the reason why the claimed method produces positive clinical results and succeeds where other methods have failed is that prior to administering T cells, patients were treated with non-myeloablative chemotherapy. The Examiner's Answer thus concludes that the non-myeloablative chemotherapy is the reason why one of ordinary skill in the art would expect that T cells that were subject to only one cycle of rapid expansion would produce clinical responses in patients.

It is improper for the Examiner to, in effect, ignore the claim limitation of administering T cells that have undergone “one cycle of rapid expansion” and conclude that non-myeloablative chemotherapy is the only reason for the success of the claimed method. Such a conclusion improperly fails to consider the claims *as a whole*, which require administering T cells which have undergone *one* cycle of rapid expansion, in addition to non-myeloablative chemotherapy as well as the other steps recited in claim 23. In determining the differences between the prior art and the claims, the question under 35 USC § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). By ignoring the claim limitation of administering T cells that have undergone “one cycle of rapid expansion” and focusing on the chemotherapy and relying on it as the sole basis for holding the Dudley Declaration to be unpersuasive and maintaining the obviousness rejection, the Examiner fails to consider the claims *as a whole*. Accordingly, the obviousness rejection cannot stand.

Moreover, *nothing* in the cited references supports the Examiner’s conclusion that the non-myeloablative chemotherapy is the reason why one of ordinary skill in the art would expect that T cells that were subject to only one cycle of rapid expansion would produce clinical responses in patients. The Examiner has not pointed to anything in the cited references that would give one of ordinary skill in the art the expectation that non-myeloablative chemotherapy would enable T cells that were subject to only *one* cycle of rapid expansion to provide the successful clinical results delineated in the Dudley Declaration, Example 1 of the instant application (see also Dudley et al. *Science* 298: 850-854 (2002) (Appeal Brief, Exhibit C; hereinafter, “Dudley 2002”), and Dudley et al., *J. Clin. Oncol.*, 26(32): 5233-5239 (2008) (Appeal Brief, Exhibit D; hereinafter, “Dudley 2008”).

On the contrary, the Appellants have provided evidence in the form of the Dudley Declaration, including two peer-reviewed journal articles referred to therein, showing that the expectation of one of ordinary skill in the art at the time the invention was made was, in fact, opposite to that which is claimed: As explained in Dudley et al., *J. Immunotherapy* 24: 363-373 (2001) (hereinafter, “Dudley 2001”) (see, e.g., p. 370, right col.; p. 371, left col.), Yee et al., *PNAS*, 99: 16168-73 (2002) (Appeal Brief, Exhibit B, hereinafter, “Yee”) (p. 16172, right col.; page 16171, right col.), and the Dudley Declaration (Dudley Dec. ¶¶ 5 - 8), the T-cells

of Dudley 2001 and Yee, which underwent *multiple* cycles of rapid expansion, failed to persist in the bloodstream of patients and provided poor objective clinical results as measured by RECIST or WHO criteria.

Clearly, the Dudley Declaration, Dudley 2001, and Yee provide evidence that the expectation of one of ordinary skill in the art at the time the instant application was filed was that T-cells that had undergone *only one* cycle of rapid expansion, as claimed, would *not* result in a positive, objective clinical response in patients (Dudley Declaration, ¶¶ 3-9). The reduction of cycles of rapid expansion from “multiple” to “one” was, therefore, contrary to logic and surprisingly resulted in a positive clinical outcome in patients.

The Dudley Declaration also shows that, contrary to the expectations of one of ordinary skill in the art, six of 13 patients that were treated with cells that had undergone one cycle of rapid expansion in Example 1 of the instant application had objective clinical responses to treatment. These results were published in Dudley 2002 (Dudley Declaration ¶ 11). The Dudley Declaration also shows that, contrary to the expectations of one of ordinary skill in the art, the study described in Dudley 2008 in which patients were treated with cells that had undergone one cycle of rapid expansion resulted in objective, clinical responses measured by RECIST criteria in 21 out of the 43 patients (48%) (see, e.g., Table 2). Thus, the Appellants have provided evidence showing that the claimed method produces positive clinical results in contrast to the expectations of one of ordinary skill in the art.

Because the claimed method provides unexpectedly superior clinical results as compared to prior art methods, the obviousness rejection cannot stand.

**B. As evidenced by the Dudley Declaration, the claimed method answers a long-felt need in the art.**

The obviousness rejection cannot stand because the Examiner has failed to consider the evidence in the form of Example 1 of the instant application, the Dudley Declaration, and the Dudley 2002 and Dudley 2008 references referred to therein that show that the claimed method answers a long-felt need in the art.

The long-felt need is evidenced in the Dudley Declaration, which shows that T-cells which underwent *multiple* cycles of rapid expansion in Dudley 2001 and Yee failed to persist in the bloodstream of patients and provided poor objective clinical results as measured by RECIST or WHO criteria (Dudley Dec. ¶¶ 5 - 8). These poor clinical results indicated a long-felt need in the art for improved adoptive immunotherapy methods for treating cancer. The answer to this long-felt need was realized with the claimed method, in which T-cells undergo *one* cycle of rapid expansion, which successfully produces positive objective clinical results in patients. This has been shown, for example, in the study described in Example 1 of the instant application (see also Dudley 2002 and Dudley 2008) (Dudley Declaration, ¶¶ 10-13).

Accordingly, the obviousness rejection cannot stand because the Examiner has failed to consider the evidence that the presently claimed method answers a long-felt need in the art to treat patients.

**C. The Dudley Declaration evidences that the claimed method succeeds where other methods have repeatedly failed.**

Example 1 of the instant application, the Dudley Declaration, and the Dudley 2002 and Dudley 2008 references referred to therein provide evidence that the claimed method succeeds where other methods have repeatedly failed. This has not been considered by the Examiner. Other methods (e.g., Dudley 2001 and Yee) that use *multiple* cycles of rapid expansion fail to persist in the bloodstream of patients and provide poor objective clinical results. In contrast, methods in which T-cells undergo one cycle of rapid expansion, as claimed, produce positive clinical results. Therefore, the claimed method succeeds where other methods have repeatedly failed.

Thus, the obviousness rejection cannot stand because the Examiner has failed to consider that the Appellants' evidence in the form of the Dudley Declaration and the Dudley 2002 and Dudley 2008 references referred to therein show that the presently claimed method succeeds where other methods have repeatedly failed.

**III. The Appellants' argument that the Examiner has failed to set forth a *prima facie* case of obviousness has not been adequately addressed.**

The Examiner has alleged that Appellants have "mainly" argued against the references individually and not against the combination of references (Examiner's Answer, page 11 ¶ 2; cf. Examiner's Answer, page 12, ¶ 3). The Examiner also alleges that the Appellants have not discussed the teaching of the secondary references U.S. Patent No. 6,447,767 to Slavin et al. (hereinafter, "Slavin") and U.S. Patent No. 5,126,132 to Rosenberg (hereinafter, "Rosenberg") that are allegedly "critical for the instant rejection" (Examiner's Answer, page 11, ¶ 3).

On the contrary, the Appellants have, indeed, shown that the combination of all of the references (including Slavin and Rosenberg) fails to teach or suggest a method of promoting the regression of a cancer in a mammal comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed in claim 23 (See (I) above, and Appeal Brief, page 4, (I), and also below). The Appellants' argument that the Examiner has failed to set forth a *prima facie* case of obviousness has not been adequately addressed.

**A. Rosenberg fails to teach administering T cells that have undergone one cycle of rapid expansion, as claimed in claim 23.**

The Examiner cites Rosenberg as allegedly teaching a general methodology of how to determine an effective amount of cells and as allegedly also teaching that the preferred amount is from about  $5 \times 10^9$  to  $5 \times 10^{11}$  (December 17, 2008 Office Action, page 4, ¶ 3 and Examiner's Answer, page 5, ¶ 1). Contrary to the Examiner's assertion, Rosenberg is not critical to the instant rejection of claim 23 because claim 23 does not recite any particular number of cells. Moreover, Rosenberg fails to cure the deficiencies of the primary references, Dudley 2001 and WO '239, because Rosenberg fails to teach administering T cells that have undergone one cycle of rapid expansion, as claimed in claim 23. Accordingly, the obviousness rejection based in whole or in part on Rosenberg cannot stand.

**B. Slavin fails to teach administering T cells that have undergone one cycle of rapid expansion, as claimed in claim 23.**

The Examiner cites Slavin as allegedly teaching administering cyclophosphamide and fludarabine prior to administering hematopoietic cells, and states the Slavin is used as a secondary reference to show that at the time the invention was made, one skilled in the art would know that administering to the mammal nonmyeloablative lymphodepleting chemotherapy was a routinely used method to induce donor specific tolerance in a method of treating cancer patients (December 17, 2008 Office Action, page 4, ¶ 2 and Examiner's Answer, pages 4-5, carryover paragraph). Contrary to the Examiner's assertion, Slavin is not critical to the instant rejection because Slavin fails to cure the deficiencies of the primary references, Dudley 2001 and WO '239, because Slavin fails to teach administering T cells that have undergone one cycle of rapid expansion, as claimed in claim 23. Accordingly, the obviousness rejection based in whole or in part on Slavin cannot stand.

Thus, the Appellants have indeed argued the combination of all of the references and have explicitly addressed Slavin and Rosenberg in the argument, contrary to the Examiner's assertion. The Examiner has failed to adequately address the Appellants' argument that a *prima facie* case of obviousness has not been set forth. Accordingly, the obviousness rejection cannot stand.

**IV. The Appellants' evidence of unexpectedly superior clinical results, long-felt need, and repeated failure of others has not been adequately addressed.**

The Examiner has failed to consider the evidence that the Appellants have presented (in the form of the Dudley Declaration, Example 1 of the specification, and the Dudley 2002 and 2008 references) that the claimed method, in which the T-cells had undergone *only one* cycle of rapid expansion, provides *unexpectedly superior clinical results* over the methods described in the cited references. The Examiner has also failed to consider the evidence that the Appellants have presented with respect to the expectations of one of ordinary skill in the art, long-felt need, and the repeated failure of other methods in the form of the Dudley Declaration and the Dudley 2001 and Yee references referred to therein. Thus, the Appellants have clearly rebutted any alleged *prima facie* case of obviousness, and the obviousness rejection cannot stand.

The Examiner's comments with respect to arguing references individually, predictability, and motivation to modify or combine references (see, e.g., December 17, 2008 Office Action, page 3, ¶¶ 1-4; page 5, ¶ 2; and page 6, ¶ 2 and Examiner's Answer, page 5, ¶ 3; page 10, ¶ 3 to page 11, ¶ 3; and page 12, ¶¶ 3-5) fail to properly consider this rebuttal evidence. Although the Examiner alleges that the addition of nonmyeloablative lymphodepleting chemotherapy does not provide surprisingly superior results, the Examiner completely fails to consider the fact that reducing the number of cycles of rapid expansion to *one*, as claimed, as opposed to increasing the number of cycles of rapid expansion, has, in fact, produced surprisingly superior, objective clinical results, contrary to the expectations of one of ordinary skill in the art. The Examiner also fails to consider that the presently claimed method answers a long-felt need and successfully treats cancer patients as compared to the repeated failure of other methods. Accordingly, the obviousness rejection cannot stand.

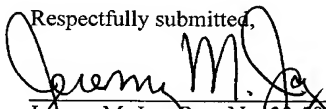
Since the final rejections of at least the sole rejected appealed independent claim are not supportable, the rejections should be withdrawn. Since all of the rejected appealed claims are commonly rejected, upon withdrawal of the rejections of appealed claim 23, appealed claims 24-40 should also be allowed.

All arguments for patentability of the claims are maintained as set forth in the Appeal Brief.

#### V. Conclusion

For the reasons set forth above, Appellants respectfully submit that the rejections of the pending claims are improper and should be reversed.

Respectfully submitted,



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